Rx Only

REJOYN™ CLINICIAN BRIEF SUMMARY

INDICATIONS FOR USE

Rejoyn is a prescription digital therapeutic for the treatment of Major Depressive Disorder (MDD) symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD age 22 years and older who are on antidepressant medication. It is intended to reduce MDD symptoms.

CONTRAINDICATION

There are no contraindications to using Rejoyn.

SAFETY INFORMATION/WARNINGS/PRECAUTIONS

Rejoyn is not intended to be used as a standalone therapy or a substitute for medication. Patients should continue their current treatment as directed.

Rejoyn does not monitor the patient's symptoms or clinical status and cannot send or receive alerts or warnings to the prescriber. Patients should be clearly instructed that if they believe their depression is worsening or if they have feelings or thoughts of harming themselves or others, to contact a healthcare professional, dial 911 or go to the nearest emergency room immediately.

PRODUCT DESCRIPTION

Rejoyn is a smartphone app-based digital therapeutic that provides 6 weeks of treatment composed of three parts: Cognitive Behavioral Therapy (CBT)-based Lessons (Lessons), Emotional Faces Memory Task (EFMT) Exercises (Exercises), and Personalized Reminders and Messaging (see Table 1). Once the 6 week treatment period is over, CBT-based Lessons are available to be revisited for an additional 4 weeks.

Table 1: Rejoyn Features, Duration, and Frequency

Core Feature	Typical Duration*	Frequency
CBT-based Lessons	3 - 4 minutes	3 times per week for 6 weeks
EFMT Exercises	11 – 26 minutes*	3 times per week for 6 weeks
Personalized Reminders and Messages	Less than 1 minute	Regularly throughout treatment

*In a clinical study of Rejoyn, a majority of EFMT Exercises were completed in this time frame. Duration will vary by individual patient.

SUPPORTED OPERATING SYSTEMS AND BROWSERS

Operating Information

Refer the patient to the app store to ensure compatibility with the patient's specific smartphone and operating system with an available internet connection. Rejoyn operates with the following operating systems:

- iOS®
- Android™

The patient should ensure their smartphone is running an OS version matching those required. If not, the patient should update the software version before downloading and using Rejoyn.

Rejoyn is not currently compatible for use with computers or tablets.

HOW TO START USING REJOYN

- Rejoyn is intended for people with MDD who are proficient in written and spoken English, have access to a smartphone, and are familiar with the use of mobile applications (apps).
- The healthcare professional will submit a prescription for Rejoyn to a designated pharmacy for fulfillment.
- The patient will download the mobile app and create an account using their mobile phone number and email address to use the app. The patient will also need to set a password for subsequent login.
- After the patient's account is created and their email address and mobile phone number are verified, an access code will be required to unlock treatment. The code will be provided by the dispensing pharmacy.
- Once the prescription access code is provided, the patient will have access to the treatment program and can begin. They should be directed to follow the instructions provided in the app.
- The patient works through the 6 week treatment program in Rejoyn by completing the Lessons and Exercises. After the end of 6 weeks, the patient has continued access to revisit the Lessons for another 4 weeks, after which the patient will no longer be able to access Rejoyn.
- The Patient Instructions For Use (IFU) can be found at Rejoyn.com and gives additional information to help the patient navigate the initial steps within the app.

Otsuka

PRODUCT DETAILS

Description

Rejoyn is a prescription app-based digital therapeutic administered via the patient's smartphone device (Apple iPhone operating system [iOS] or Android operating system [OS]). The app delivers a proprietary, interactive cognitive-emotional and behavioral therapeutic intervention. The core components of Rejoyn are the brief CBT-based Lessons to learn and apply key therapeutic skills, EFMT Exercises, and personalized reminders and messaging to reinforce the Lesson content and encourage engagement.

The first component of Rejoyn is a series of CBT-based Lessons incorporating principles of emotion regulation (ER), behavioral activation (BA), and cognitive restructuring (CR) designed to be internalized and acted on. Each Lesson consists of a short, animated video describing the main CBT principle, followed by either a prompt encouraging engagement with an out-of-app activity or a guided audio psychotherapy exercise (referred to as 'Toolkit' in the app).

The second component of Rejoyn is a series of EFMT Exercises. Each EFMT Exercise is a working memory task that involves human facial expressions of emotion as the stimuli and recall of the emotion displayed on the face as the response. The app is responsive to the patient's memory performance and adjusts to keep the exercise challenging and engaging. The EFMT exercise is set up as an N-back memory task, which requires patients to decide Yes/No whether a facial emotion shown in a sequence matches that which appeared "n" items ago, from 1-back (minimal demand) to 7-back (high demand). EFMT utilizes 4 emotions (happiness, sadness, surprise, and disgust) for the exercise.

Rejoyn also includes personalized reminders and text messages that reinforce the skills taught in the Lessons and encourage completion of the program.

Using Rejoyn

The Rejoyn active treatment period involves 6 weeks of alternating CBT-based Lessons and EFMT Exercises with regular text messages to reinforce Lesson content and encourage completion of the program. Once the 6 week treatment period is over, CBT-based Lessons are available to be revisited for an additional 4 weeks. An illustration of the recommended treatment schedule is shown in Table 2.

Table 2: Recommended Treatment Schedule

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 1	Lesson 1	Exercise 1	Lesson 2	Exercise 2	Lesson 3	Exercise 3	Rest
Week 2	Lesson 4	Exercise 4	Lesson 5	Exercise 5	Lesson 6	Exercise 6	Rest
Week 3	Lesson 7	Exercise 7	Lesson 8	Exercise 8	Lesson 9	Exercise 9	Rest
Week 4	Lesson 10	Exercise 10	Lesson 11	Exercise 11	Lesson 12	Exercise 12	Rest
Week 5	Lesson 13	Exercise 13	Lesson 14	Exercise 14	Lesson 15	Exercise 15	Rest
Week 6	Lesson 16	Exercise 16	Lesson 17	Exercise 17	Lesson 18	Exercise 18	Rest
4 Weeks Continued Access	Option to revisit Lessons 1-18 at any time						

*Lesson refers to CBT-based Lessons
**Exercise refers to EFMT Exercises

As it is anticipated that some patients might miss an activity on a certain day or otherwise get behind relative to the recommended schedule, flexibility is built into the program. As the program unfolds, patients can complete one Lesson and one Exercise per day to either get ahead or catch up to the schedule but cannot do more than one of each on a given day. The next tasks are 'unlocked' at midnight on the day they become available. The app interface will show the patient the next scheduled tasks, including an indication of when any locked tasks will become available. This schedule of three Lessons and three EFMT Exercises continues for six weeks, resulting in a total of 18 Lessons and 18 Exercises. Table 3 shows an example of an alternate treatment schedule where the patient starts their treatment in the middle of the week and 'doubles' up tasks on some days.

At the end of each week, any remaining Lessons are unlocked so the patient can view them, but the previous week's Exercises will not be available. The pivotal Mirai Trial (detailed below) demonstrated the value of adherence in relation to efficacy outcomes, so it is recommended that patients complete as many of the scheduled tasks per week as they are able.

Table 3: Alternate Treatment Schedule (Example)

	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday
Week 1	Lesson 1 Exercise 1			Lesson 2 Exercise 2	Lesson 3 Exercise 3		
Week 2		Lesson 4	Exercise 4	Lesson 5 Exercise 5	Lesson 6 Exercise 6		
Week 3		Lesson 7 Exercise 7		Lesson 8 Exercise 8		Lesson 9	Exercise 9
Week 4	Lesson 10	Exercise 10		Lesson 11		Exercise 11	Lesson 12 Exercise 12
Week 5				Lesson 13 Exercise 13	Lesson 14 Exercise 14	Lesson 15	Exercise 15
Week 6		Lesson 16 Exercise 16		Lesson 17 Exercise 17	Lesson 18 Exercise 18		
4 Weeks Continued Access	Option to revisit Lessons 1-18 at any time						

*Lesson refers to CBT-based Lessons

**Exercise refers to EFMT Exercises

CLINICAL EVIDENCE

Data suggest that deficits in working memory for emotional material are associated with cognitive inflexibility and underlie ruminative responses in MDD.[1] Neuroimaging trials of emotional information-processing and emotion regulation demonstrate that relative to healthy controls, individuals with MDD show hyperactivation of limbic neural systems implicated in emotion perception and responses (e.g., amygdala) and an associated hypoactivation of cortical systems responsible for cognitive control and ER (e.g., dorsal, ventrolateral, and medial prefrontal cortex [PFC]).[2] Subcortical systems involved in emotion perception and generation of negative affect (e.g., the amygdala) have long been a focus of research in MDD.[3,4] Prefrontal cortex (PFC) structures involved in regulation of emotion and cognitive control are emerging as critical to the disease state and antidepressant response.[5]

Mechanism of Action for Rejoyn

The mechanism of action (MOA) of Rejoyn in the treatment of MDD is hypothesized to be mediated through a complementary combination of CBT-based Lessons and EFMT Exercises.

CBT is a well-established approach to treating MDD whether delivered in-person or via digital formats. The CBT-based Lessons in Rejoyn focus on the key principles of CR (cognitive restructuring - observing and re-framing maladaptive cognitions such as cognitive distortions), BA (behavioral activation - deliberately increasing goal-directed behavior, physical activity, and interpersonal interaction) and ER (emotional regulation - an individual's ability to modulate or control the influence an emotion has on them, or to modulate the degree to which an emotion is experienced).[6,7] Using these key principles, the brief lessons target the most common symptoms

of MDD by encouraging conscious reflection on thought and behavior patterns with the goal of developing alternate interpretations of experience and shifting toward healthier thought and behavior patterns.

The EFMT is a form of cognitive emotional training designed to enhance cognitive control over emotional information processing by targeting the two key regions of neural networks involved in affective disorders: (i) the amygdala which is activated upon identification of facial emotions and (ii) the dorsolateral prefrontal cortex (DLPFC) which is activated upon recall of emotional stimuli.[8,9]

Two randomized controlled proof-of-concept trials on EFMT in unmedicated patients support the hypothesis that these changes could have antidepressant effects by improving emotion regulation and reducing perseverative thinking.[10,11] A follow-up single-arm neuroimaging study with participants who completed the 6 week EFMT regimen found that the working memory-induced connectivity from cognitive control regions (right DLPFC and bilateral dorsal anterior cingulate cortex [dACC]) to the right amygdala was modulated, and this modulation was associated with symptomatic improvement.[12] This preliminary evidence suggests that the benefits of EFMT may be associated with changes in plasticity of brain networks implicated in MDD.[12]

Clinical Trial

The indications for use are supported by the results from the Mirai Trial, a pivotal, multicenter, remote, double-blinded (patients also blinded to hypothesis), randomized controlled trial in adult participants diagnosed with MDD who were on antidepressant therapy (ADT) for the treatment of depression.

Study Population

The study enrolled patients from 22 to 64 years with a current primary diagnosis of MDD based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Patients were eligible if they had a 17-item Hamilton Rating Scale for Depression (HAM-D17) total score ≥ 18 at screening and the baseline visit (Day 1) and reported an inadequate response to their current ADT treatment, defined as <50% reduction in depression symptom severity in the current major depressive episode of MDD. Key exclusion criteria included (1) a lifetime diagnosis of psychotic or bipolar disorders, (2) current diagnosis of posttraumatic stress disorder (PTSD), panic disorder, obsessive compulsive disorder (OCD), or substance or alcohol use disorder, (3) inadequate response to more than one ADT for the current major depressive episode, (4) treatment at any time with psychopharmacological augmentation therapies such as atypical antipsychotics, ketamine, esketamine, or arketamine for depression, electroconvulsive therapy (ECT), neuromodulation devices (e.g., transcranial magnetic stimulation [TMS], vagal nerve stimulation [VNS]), or treatment with psychotherapy within 90 days prior to screening, (5) characterization as treatment refractory by the study investigator based on presentation or history, and (6) a significant risk of suicide.

Trial Design

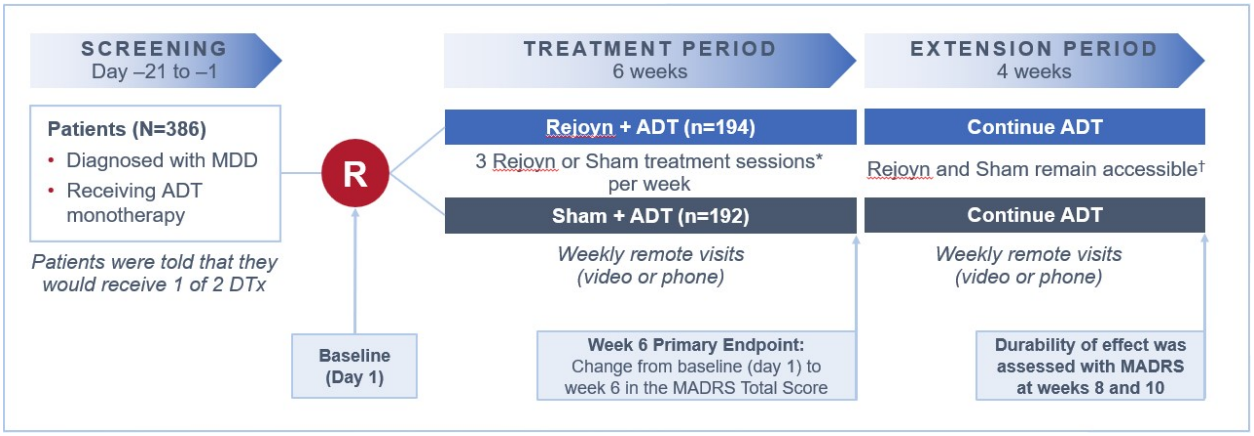
Participants took part in the trial for up to 13 weeks, including a 3-week screening period, a 6 week treatment period, and a 4-week extension period (see Figure 1).

On Day 1 of the treatment period, eligible participants were randomized to Rejoyn or a Sham app in a 1:1 ratio. Rejoyn consisted of the components described above and in the current product. The Sham app included a cognitive training exercise called the Shapes Memory Task (SMT), designed to be a working memory task analogous in structure and matched to the EFMT for time, attention, and participant expectation of therapeutic effect.

Each Sham treatment session consisted of a SMT exercise and did not include CBT-based Lessons or EFMT Exercises. Participants in both groups received personalized reminders and text messages to maintain engagement throughout the study duration. During the treatment period (Day 1 [baseline] to Week 6), participants had remote telehealth visits from Weeks 1 through 6. Participants were expected to adhere to their app exercises during the treatment period, and adherence was monitored. Investigators followed up with participants in both groups who missed sessions and provided reminders to adhere to the session schedule.

After Week 6, participants continued in the trial during the extension period (Weeks 7 to 10) to assess durability of effect. Participants had remote telehealth visits from Weeks 7 through 10. EFMT and SMT exercises were not available during this period, however, participants continued to receive supportive text messages. Participants in the Rejoyn arm retained access to previous CBT-based Lessons and tools. No new therapeutic content was introduced during the extension period.

Figure 1. Mirai Trial Design



*A Rejoyn treatment session was defined as 1 EFMT Exercise (also known as a Brain Exercise) and 1 CBT-based Lesson (also known as a Therapeutic Lesson). A Sham treatment session was defined as 1 SMT exercise.

†EFMT and SMT exercises were not available during the extension period. Patients in the EFMT arm could continue to access the CBT-based Lessons. Patients in both arms continued to receive text messages.

ADT, antidepressant therapy; CBT, cognitive behavioral therapy; DTx, digital therapeutics; EFMT, Emotional Faces Memory Task; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SMT, Shapes Memory Task.

Outcome Measures

The primary objective of the Mirai Trial was to evaluate the effectiveness of Rejoyn in reducing depressive symptoms compared with Sham control. The primary efficacy endpoint was the change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. This was evaluated in the Modified Intent-To-Treat (mITT) (primary) and ITT populations. A secondary effectiveness endpoint to evaluate the durability of the effect of Rejoyn was assessed during the extension period (Weeks 7 to 10). Because the content of Rejoyn and Sham differed and specific reference to the content of the software had the potential to unmask trial staff, various measures were undertaken to ensure adequate masking. For example, ratings were conducted for the primary efficacy endpoint (MADRS) by independent, remote, blinded raters who had no access to the study protocol or clinical information other than what was solicited for the MADRS rating.

Clinical assessments used to evaluate secondary and exploratory effectiveness endpoints also included patient-reported outcomes, such as the Patient Health Questionnaire-9 (PHQ-9), the clinician rated Clinical Global Impressions-Severity Scale (CGI-S), and the Generalized Anxiety Disorder-7 (GAD-7).

The primary efficacy endpoint was tested at a significance level of 0.049. All other efficacy endpoints, including secondary, exploratory, and post hoc efficacy endpoints, were tested at a nominal 0.05 level (2 sided) without adjusting for multiplicity.

Participant Disposition

Table 4 summarizes the various analysis sets used in the Mirai Trial. Of the 1034 participants screened, 386 were enrolled and randomized to the Rejoyn (N =194) or Sham app (N = 192) treatment groups (Intent-To-Treat [ITT]). The demographic characteristics (randomized sample) are shown in Table 5. The mITT population comprised 354 participants (N = 177 from both groups) who had 1 session with either treatment and assessments of MADRS total score at both baseline and at least 1 post-baseline timepoint. The Safety Sample comprised 373 participants (Rejoyn: N = 187; Sham: N = 186) who received at least 1 treatment session with either Rejoyn or Sham. Baseline mean psychiatric evaluation scores for mITT are shown in Table 6.

Table 4: Mirai Trial Analysis Sets			
		Sample Size	
Analysis Set	**Description**	**Rejoyn**	**Sham**
Intent-To-Treat (ITT)	All randomized patients	194	192
Modified Intent-To-Treat (mITT)*	Randomized patients with 1 treatment session (Rejoyn or Sham) and MADRS assessment at baseline and ≥ 1 post-baseline timepoint	177	177
Safety Sample	Randomized patients with ≥ 1 treatment session (Rejoyn or Sham)	187	186

*mITT defined as Full Analysis Set (FAS) in protocol

Table 5: Demographic Characteristics (Randomized Sample)			
Demographic Characterstic	**Rejoyn (N=194)**	**SHAM (N=192)**	**TOTAL (N=386)**
Age (yrs)			
n	194	192	386
Mean (SD)	43.0 (12.1)	42.2 (12.1)	42.6 (12.1)
Median	43.0	41.0	42.0
Min, Max	22,64	22,64	22,64
Sex [n (%)]			
Male	29 (14.9%)	25 (13.0%)	54 (14.0%)
Female	165 (85.1%)	167 (87.0%)	332 (86.0%)
Race [n (%)]			
White	141 (72.7%)	160 (83.3%)	301 (78%)
Black or African American	36 (18.6%)	25 (13.0%)	61 (15.8%)
American Indian or Alaska Native	5 (2.6%)	1 (0.5%)	6 (1.6%)
Asian	5 (2.6%)	4 (2.1%)	9 (2.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	7 (3.6%)	2 (1.0%)	9 (2.3%)
Ethnicity			
Hispanic or Latino	20 (10.3%)	16 (8.3%)	36 (9.3%)
Not Hispanic or Latino	173 (89.2%)	174 (90.6%)	347 (89.9%)
Unknown	1 (0.5%)	2 (1.0%)	3 (0.8%)
Cannabis Use [n (%)]			

Yes	11 (5.7%)	24 (12.5%)	35 (9.1%)
No	183 (94.3%)	168 (87.5%)	351 (90.9%)

Max = maximum; Min = minimum

Table 6: Baseline Mean Psychiatric Evaluation Scores (ITT and mITT)

	ITT			mITT		
	Rejoyn	**Sham**	**Total**	**Rejoyn**	**Sham**	**Total**
MADRS	28.4	28.5	28.4	28.5	28.4	28.4
GAD-7	9.5	9.7	9.6	9.6	9.6	9.6
CGI-S	4.3	4.3	4.3	4.3	4.3	4.3
PHQ-9*	15.4	15.2	15.3	15.3	15.1	15.2
HAM-D17	22.7	22.4	22.5	22.8	22.3	22.6

* PHQ-9 assessed at screening.

Safety

Adverse events were directly assessed via phone or video based on the trial being conducted remotely. Adverse events were determined to be related or unrelated to Rejoyn by the investigator. No Treatment Emergent Adverse Event (TEAE) was assessed as related to Rejoyn during the trial. There were no discontinuations due to TEAEs. There was 1 discontinuation due to lack of efficacy in the Sham group. No serious TEAEs occurred during the treatment period. One serious TEAE of transient ischemic attack (assessed as not related to Rejoyn) was reported during the extension period.

The most common TEAEs during the treatment period (all nonserious and not related to Rejoyn) were upper respiratory tract infection (1.1% [n = 2] and 3.2% [n = 6] in Rejoyn and Sham, respectively), nasopharyngitis (1.1% [n = 2] and 2.7% [n= 5] in Rejoyn and Sham, respectively), and headache (2.1% [n = 4] and 1.6% [n = 3] in Rejoyn and Sham, respectively). Headache was the only TEAE that was experienced by at least 2% of subjects in the Rejoyn group at an incidence rate greater than Sham.

During the treatment period, one subject in the Rejoyn group experienced worsening depressive symptoms (based on predefined protocol criteria). In the Rejoyn group, 3.21% (n = 6) of subjects reported clinically important suicidality (based on predefined protocol criteria), compared to 4.84% (n = 9) of subjects in the Sham group. During the extension period, 0.53% (n = 1) of subjects in the Rejoyn group and 1.08% (n = 2) of subjects in the Sham group had clinically important suicidality.

Efficacy Summary

Overall data from the Mirai Trial indicate that Rejoyn provides benefit to participants with MDD as an adjunct to antidepressant medication. The effectiveness endpoints for both the ITT and mITT populations showed consistent results across patient and clinician-rated scales (see Table 7).

Table 7: Efficacy Endpoints in ITT and mITT Populations

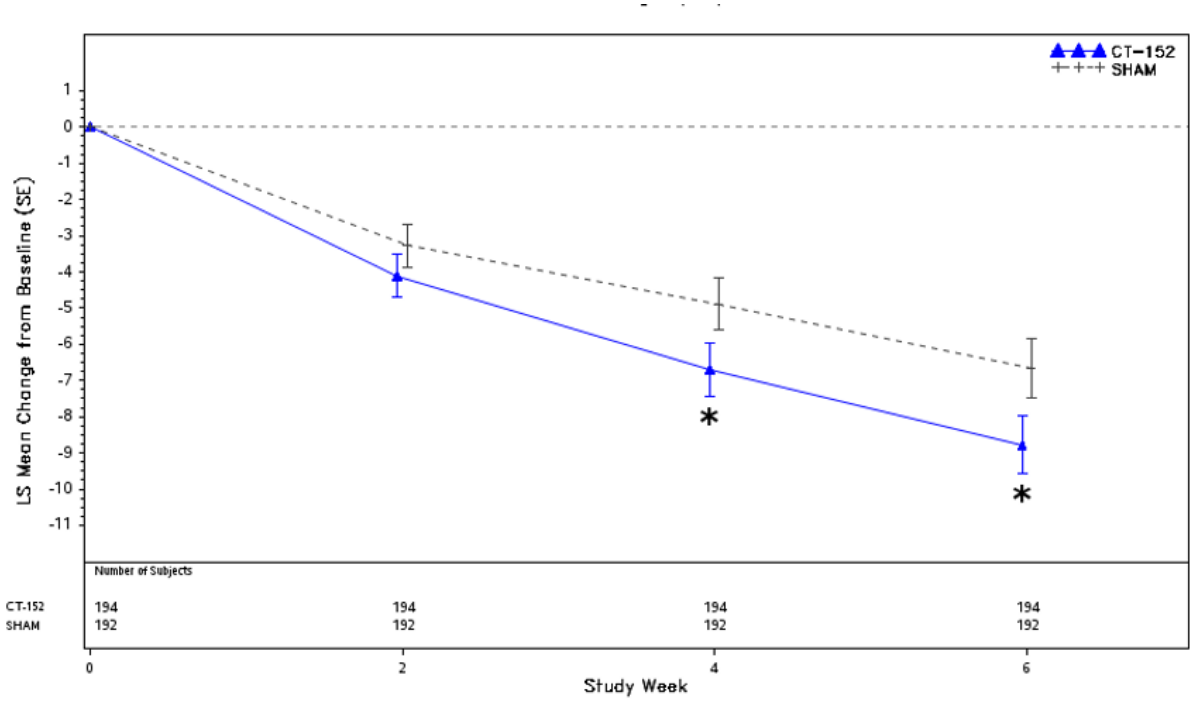
	ITT				mITT*			
Outcome Measure	**Rejoyn**	**Sham**	**Between-Group Δ**	**P-value**	**Rejoyn**	**Sham**	**Between-Group Δ**	**P-value**
MADRS								
Change in Total Score from Baseline to Week 6	-8.78	-6.66	-2.12	0.0211†	-9.03	-7.25	-1.78	0.0568
Full or Partial Response‡	51.3%	38.7%	1.32 RR	0.0191†	48.3%	37.5%	1.27 RR	0.0485†
Full Response§	30.4%	20.2%	1.49 RR	0.0331†	28.4%	20.4%	1.38 RR	0.0884
Partial Response¶	20.9%	18.6%	1.14 RR	0.5619	19.9%	17.0%	1.15 RR	0.5342
Remission#	18.2%	13.0%	1.39 RR	0.1934	17%	13.6%	1.24 RR	0.3901
PHQ-9	-6.93	-5.15	-1.78	0.0012††	-6.68	-5.10	-1.58	0.0029††
CGI-S	-1.03	-0.74	-0.29	0.0037††	-1.06	-0.80	-0.26	0.0098††

*mITT defined as Full Analysis Set (FAS) in protocol and used for the primary efficacy endpoint analysis
† P-value < 0.05
†† P-value < 0.01
‡≥30% Reduction from baseline at Week 6
§≥50% Reduction from baseline at Week 6
¶≥30%-50% Reduction from baseline at Week 6
#≥50% Reduction from baseline and MADRS <10 at Week 6

Primary Efficacy Endpoint: MADRS

Data from the Mirai Trial indicate that Rejoyn provides benefit to participants with MDD as an adjunct to antidepressant medication. In the ITT analysis performed on the randomized population using the multiple imputation method, the mean change from baseline to Week 6 in the MADRS total score in the ITT was -8.78 in the Rejoyn group compared with -6.66 in the Sham group, which yielded a group difference of -2.12 (p = 0.0211, 95% CI [-3.93, -0.32]) (see Figure 2). The mean MADRS total score at baseline and scheduled visits during the treatment period for the ITT population is presented in Figure 3. The mean change from baseline to Week 6 in the MADRS total score in the mITT was - 9.03 in the Rejoyn group compared with -7.25 in the Sham group, which yielded a group difference of -1.78 (p = 0.0568, 95% CI [-3.60, 0.05]), which was not statistically significant because the final p-value did not meet the pre-specified threshold of 0.049 (see Figure 4). The mean MADRS total score at baseline and scheduled visits during the treatment period for the mITT population is presented in Figure 5.

Figure 2: LS Mean Change from Baseline During the Treatment Period in MADRS Total Score, MMRM (ITT)

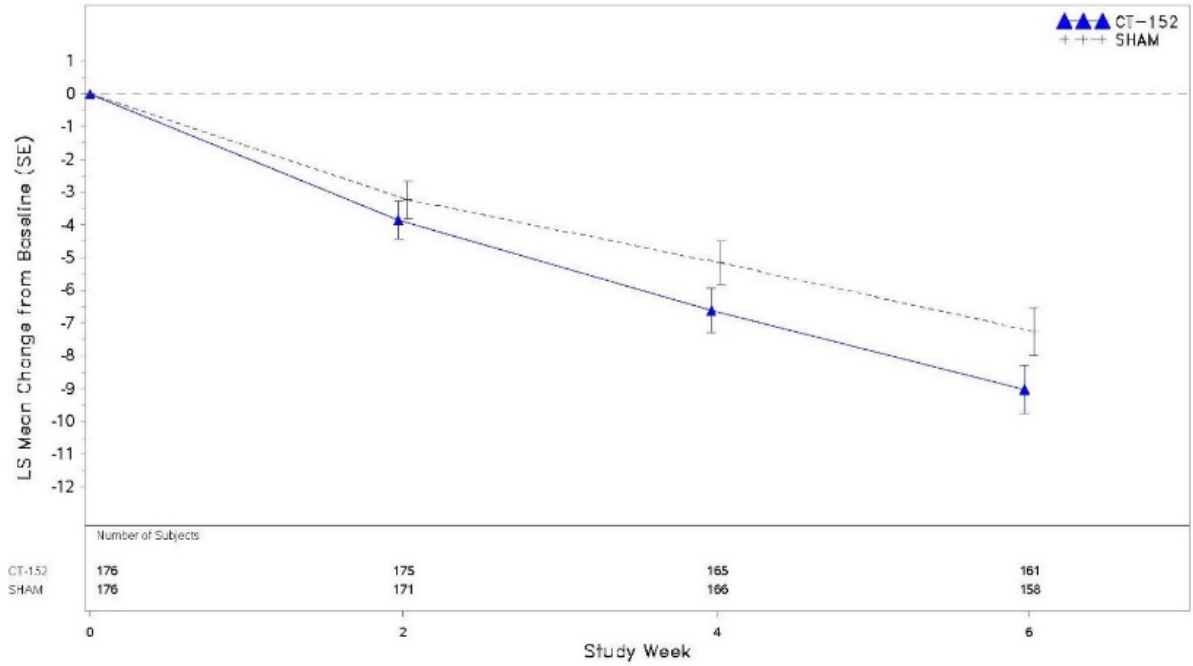


* P-value < 0.05
Note: Error bars are LS Mean +/- one SE.

Figure 3: Mean MADRS Total Score at Baseline and Scheduled Visits During the Treatment Period (ITT)

PLACEHOLDER

Figure 4: LS Mean Change from Baseline During the Treatment Period in MADRS Total Score, MMRM (mITT)



Note: Error bars are LS Mean +/- one SE.

Figure 5: Mean MADRS Total Score at Baseline and Scheduled Visits During the Treatment Period (mITT)

PLACEHOLDER

MADRS Response and Remission Rates

In addition to primary and secondary endpoints, the Mirai Trial included exploratory endpoints to determine the percentage of subjects in each group who achieved a: (1) Full or Partial Response (defined as ≥ 30% reduction in MADRS total score from baseline to Week 6); (2) Full Response (defined as ≥ 50% reduction in MADRS total score from baseline to Week 6); (3) Partial Response (defined as ≥ 30% and < 50% reduction in MADRS total score from baseline to Week 6); and (4) Remission (defined as ≥ 50% reduction in MADRS total score from baseline to Week 6 and MADRS total score of 10 or less). In the ITT analysis performed on the randomized population using the multiple imputation method, compared with the Sham group, patients in the Rejoyn group demonstrated numerically greater Full or Partial response rate (51.3% compared to 38.7%, respectively; p = 0.0191), Full Response Rate (30.4% compared to 20.2%, respectively; p = 0.0331), Partial Response Rate (20.9% compared to 18.6%, respectively; p = 0.5619), and Remission Rate (18.2% compared with 13%, respectively, p = 0.1934).

In the mITT analysis performed on the randomized population using the multiple imputation method, compared with the Sham group, patients in the Rejoyn group demonstrated a numerically greater Full or Partial Response rate (48.3% compared with 37.5%, respectively; p = 0.0485), Full Response Rate (28.4% compared with 20.5%, respectively; p = 0.0884), Partial Response Rate (19.9% compared to 17.0%, respectively, p = 0.5342), and Remission Rate (17.0% compared with 13.6%, respectively; p = 0.3901).

Analysis of Within-Patient Changes

A post-hoc analysis was conducted to determine the improvement in the MADRS score that represents meaningful within-patient change (MWPC) thresholds for symptom benefit using an anchor-based approach in the mITT population. An anchor-based approach defines a responder by exploring the associations between the primary endpoint instrument, MADRS, and other instruments used in the trial, CGI-S and PHQ-9, for which meaningful treatment differences are more easily/directly interpretable or already known.[14] An 8-point and 10-point reduction in MADRS were identified as appropriate MWPC thresholds (see Table 8). From baseline to Week 6, 50.3% of patients in the Rejoyn group met or exceeded the 8-point threshold compared with 44.9% of patients in the Sham group (see Table 8). This 5.4% between-group difference indicates patients in the Rejoyn group were 24% more likely to achieve an 8-point improvement (odds ratio [OR] [95% CI] = 1.24 [0.799, 1.927]) and 12% more likely to experience this improvement (relative risk [RR] [95% CI] = 1.12 [0.889, 1.411]) compared with patients in the Sham group.

When applying the higher MWPC threshold of a 10-point improvement in the MADRS score from baseline to Week 6, 44.7% of patients in the Rejoyn group met or exceeded this threshold, compared with 35.4% of patients in the Sham group (see Table 8). This 9.3% between-group difference indicates patients in the Rejoyn group had 47% greater odds of achieving a 10-point improvement (OR [95% CI] = 1.47 [0.939, 2.312]) and were 26% more likely to experience this improvement (RR [95% CI] = 1.26 [0.962, 1.656]) compared with patients in the Sham group.

When viewed graphically in Figure 6, there is clear separation at the MWPC thresholds of 8-point and 10-point improvement in MADRS and the cumulative proportion of responders is

higher across the improvement (negative) values of MADRS for the Rejoyn group relative to Sham. This suggests that a greater proportion of patients in the Rejoyn group observed a meaningful symptom benefit compared with the Sham group.

As stated above, this anchor-based MWPC analysis and responder comparisons are part of a post-hoc analysis, and therefore, should be interpreted with caution.

Table 8: Proportions of MADRS Responders at 8-Point and 10-Point Minimum Within-Patient Change Improvement Thresholds by Treatment Group at Week 6 (mITT)

MWPC MADRS* Improvement Threshold	Status†	Statistic	Rejoyn	Sham	Total
8-points		N	161	158	319
	Improved	n (%)	81 (50.31)	71 (44.94)	152 (47.65)
	Not Improved	n (%)	80 (49.69)	87 (55.06)	167 (52.35)
		n missing	16	19	35
		OR (95% CI)‡	1.24 (0.799, 1.927)		
		RR (95% CI)‡	1.12 (0.889, 1.411)		
10-points		N	161	158	319
	Improved	n (%)	72 (44.72)	56 (35.44)	128 (40.13)
	Not Improved	n (%)	89 (55.28)	102 (64.56)	191 (59.87)
		n missing	16	19	35
		OR (95% CI)‡	1.47 (0.939, 2.312)		
		RR (95% CI)‡	1.26 (0.962, 1.656)		

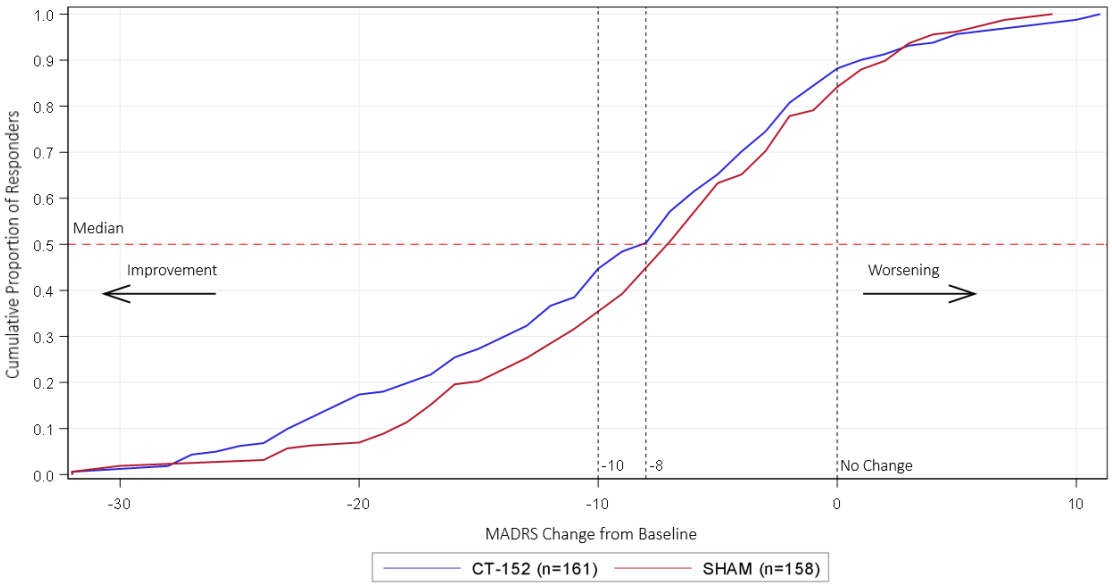
MWPC = minimum within-patient change; OR = odds ratio; RR = relative risk

*Higher MADRS scores indicate more severe depressive symptoms; negative change scores indicate improvement.

†Improvement was defined as a change in MADRS score from baseline that met or exceeded the defined MWPC threshold in the direction of improvement (negative change from baseline). All other patients were classified as not improved.

‡Odds ratio (OR) and relative risk (RR) are calculated for improved versus no change/not improved

Figure 6: Empirical Cumulative Distribution Function (eCDF) of the MADRS Total Score Change from Baseline at Week 6 by Treatment; Population (N=354) (mITT)

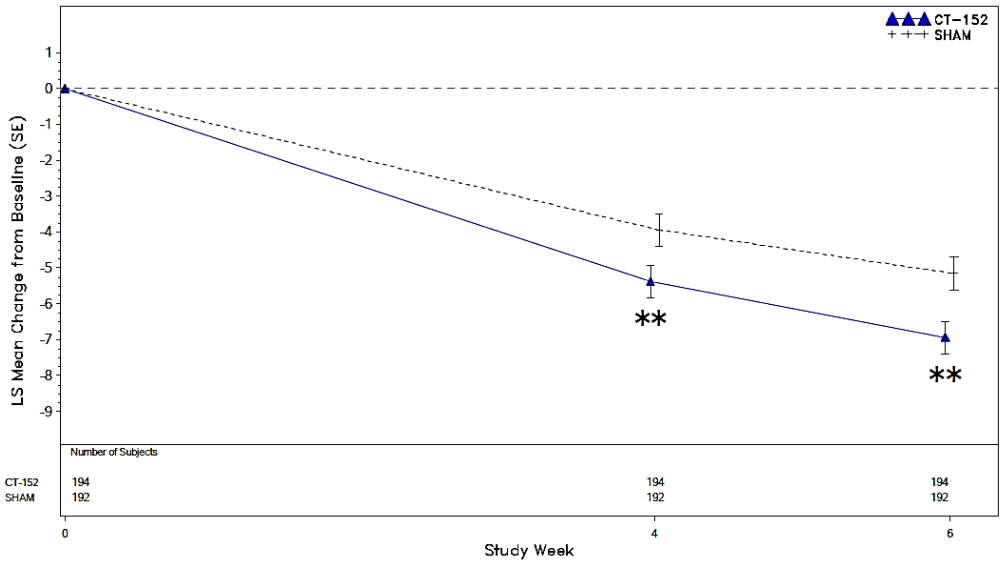


PHQ-9 and CGI-S

MADRS data were supported by a clinician assessment of global symptom severity (CGI-S) and a participant-reported outcome scale of depression (PHQ-9).

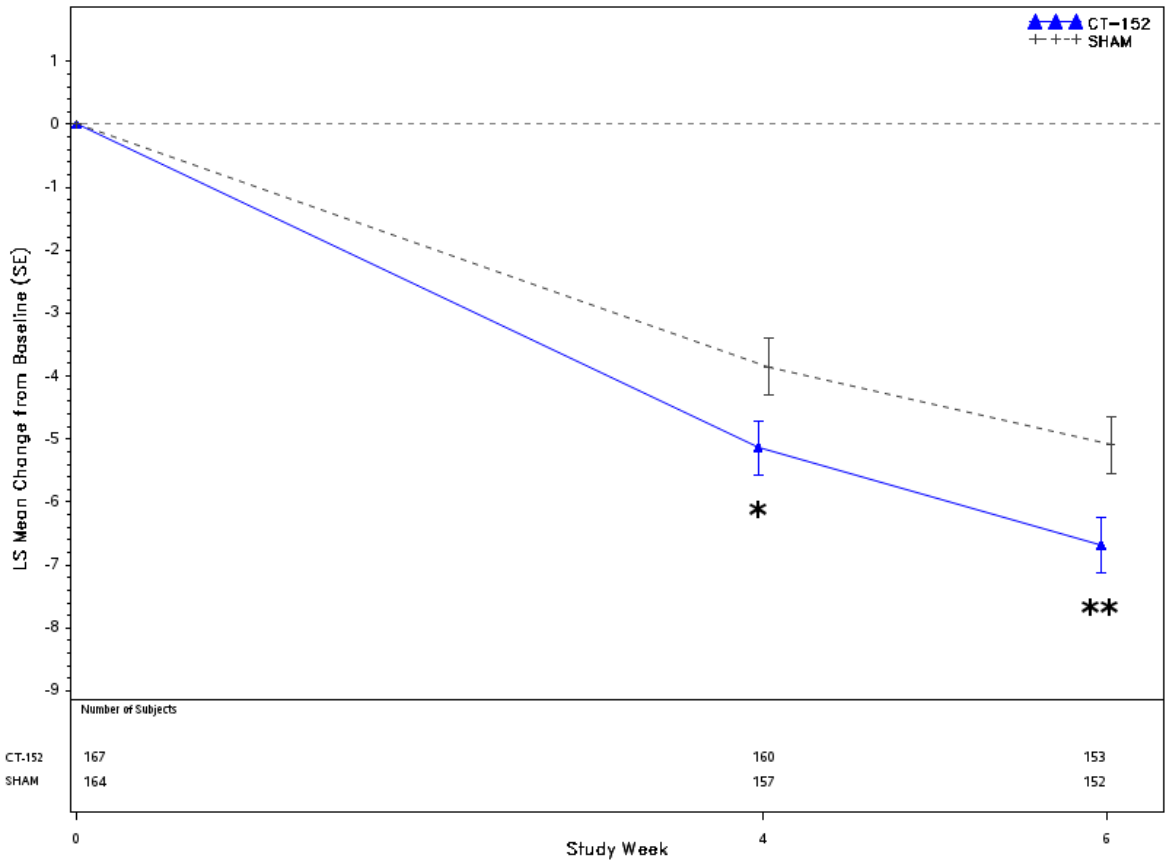
The mean change from baseline to Week 6 in the PHQ-9 total score in the ITT population was - 6.93 in the Rejoyn group compared with -5.15 in the Sham group, which yielded a group difference of -1.78 (p = 0.0012 CI [-2.85, -0.71]) (see Figure 7). The mean change from baseline to Week 6 in the PHQ-9 total score in the mITT population was -6.68 in the Rejoyn group compared with -5.10 in the Sham group, which yielded a group difference of -1.58 (p = 0.0029, CI [-2.62, -0.54]) (see Figure 8). The mean within-group change in the Rejoyn group, in both the ITT and mITT populations represents a clinically meaningful and a categorical improvement from “moderately severe” to “mild”.[13,14] In the Sham group, the mean within-group change in both the ITT and mITT populations also represents a clinically meaningful change, associated with a categorical improvement from “moderately severe” to “moderate”.[15]

Figure 7: LS Mean Change from Baseline During Treatment Period in PHQ-9 Total Score, MMRM (ITT)



** P-value < 0.01
Note: Error bars are LS Mean +/- one SE.

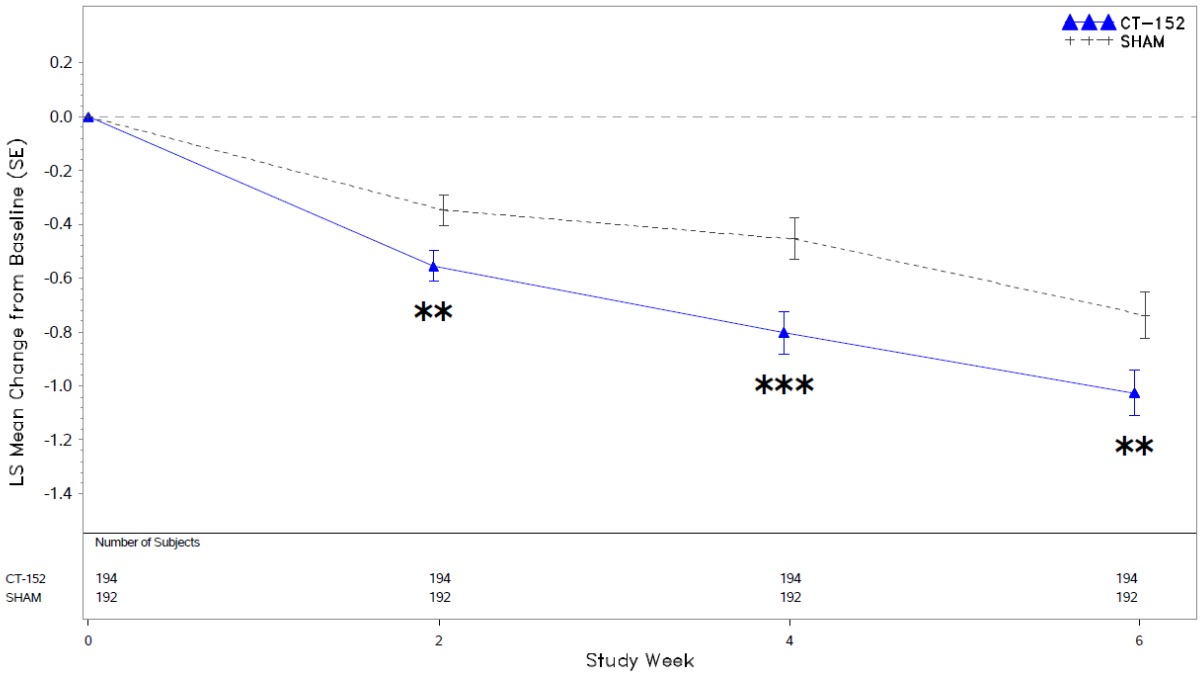
Figure 8: LS Mean Change from Baseline During Treatment Period in PHQ-9 Total Score, MMRM (mITT)



* P-value < 0.05, ** P-value < 0.01
Note: Error bars are LS Mean +/- One SE. Note: The PHQ-9 baseline was obtained at the screening visit.

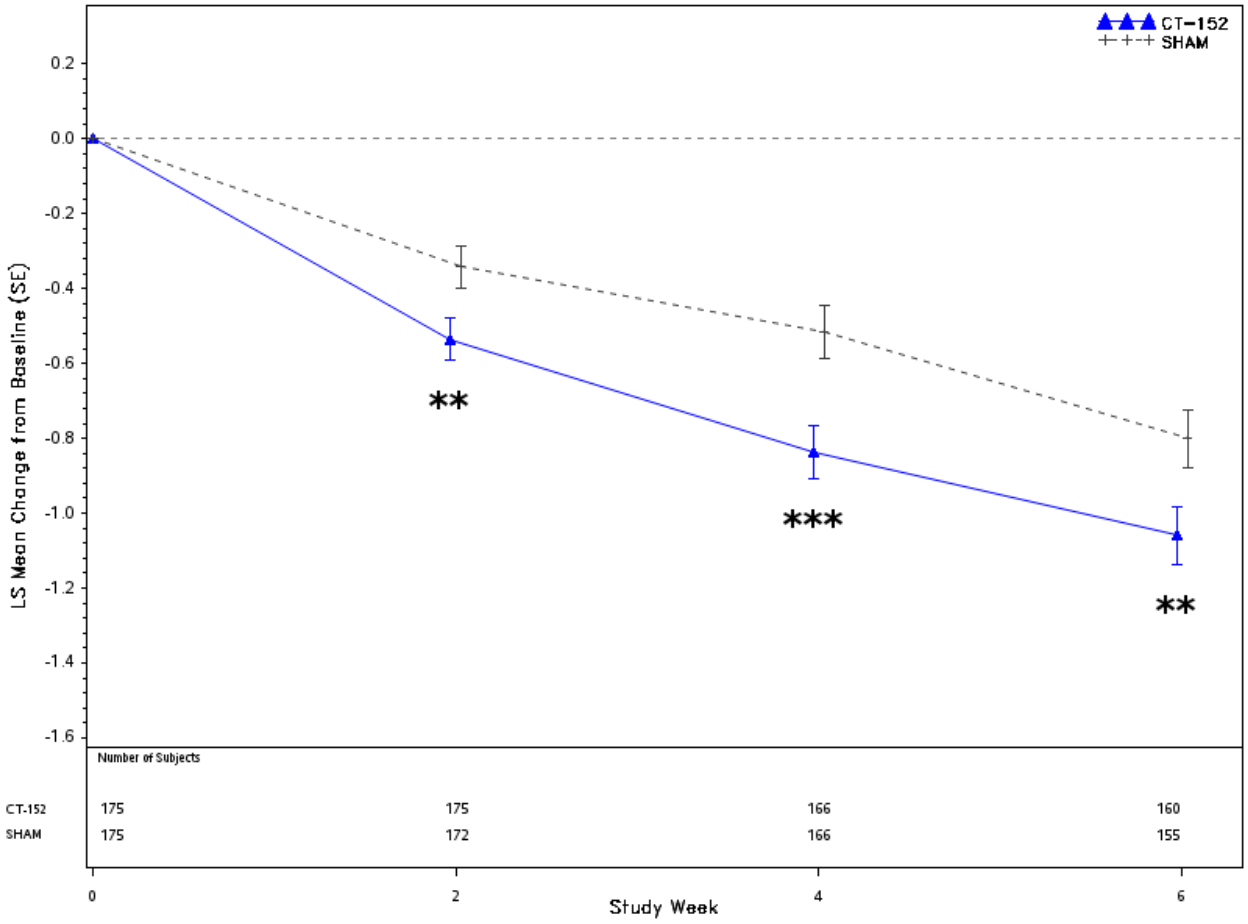
The mean change from baseline to Week 6 in the CGI-S total score in the ITT population was -1.03 in the Rejoyn group compared with -0.74 in the Sham group, which yielded a group difference of -0.29 (p = 0.0037, 95% CI [-0.48, -0.09]) (see Figure 9). The mean change from baseline to Week 6 in the CGI-S total score in the mITT population was -1.06 in the Rejoyn group compared with -0.8 in the Sham group, which yielded a group difference of -0.26 (p = 0.0098, 95% CI [-0.46, -0.06]) (see Figure 10). The mean within-group change in the CGI-S, in both the ITT and mITT populations represents a clinically meaningful and a categorical improvement from “moderately ill” to “mildly ill”.[13]

Figure 9: LS Mean Change from Baseline During Treatment Period in CGI-S Score, MMRM (ITT)



** P-value < 0.01, *** P-value < 0.001
Note: Error bars are LS Mean +/- one SE.

Figure 10: LS Mean Change from Baseline during Treatment Period in CGI-S Score, MMRM (mITT)



** P-value < 0.01, *** P-value < 0.001
Note: Error bars are LS Mean +/- One SE.

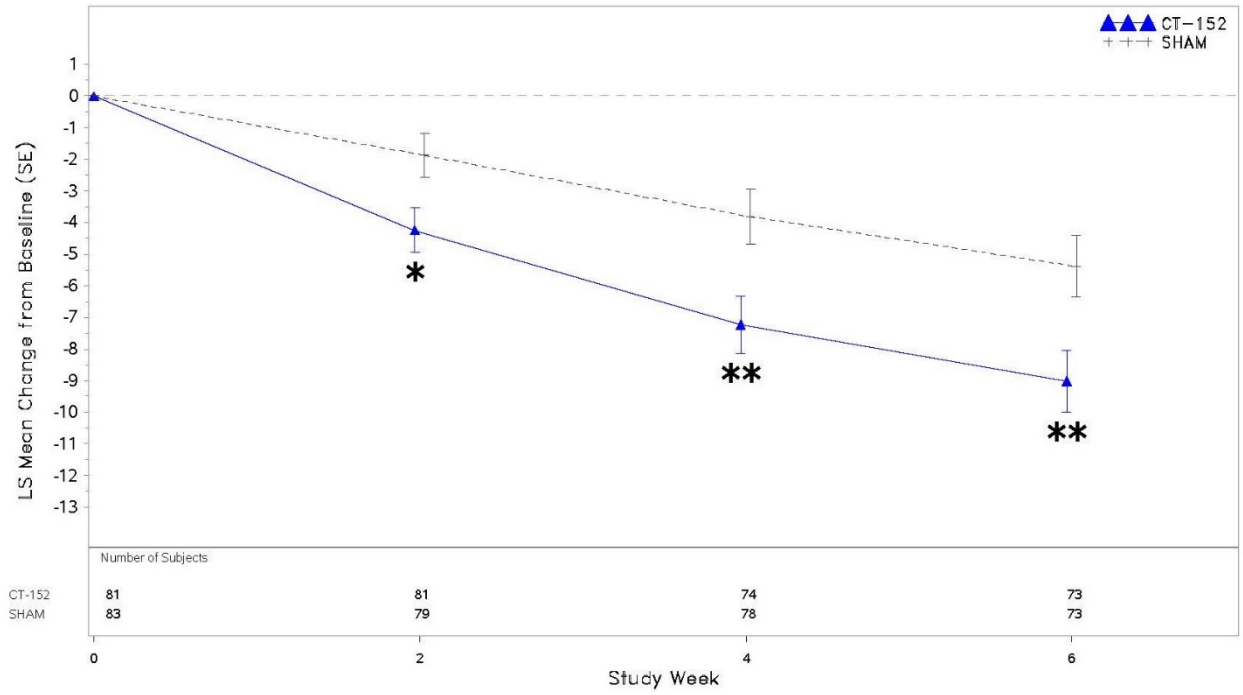
GAD-7

An additional analysis was conducted in the mITT population to assess the change from baseline to Week 6 in GAD-7 total score for Rejoyn versus Sham. The mean change from baseline to Week 6 in the GAD-7 total score was -3.41 in the Rejoyn group compared with - 2.64 in the Sham group, which yielded a group difference of -0.77 (p = 0.0705, 95% CI [-1.61, 0.07]).

MADRS Anxious Subgroup

Several pre-planned analyses were conducted in the mITT population based on baseline symptom severity. In an analysis of participants with moderate or higher anxiety symptoms at baseline, defined as a score of 10 or greater on the GAD-7, early and sustained treatment effects were observed. The mean change from baseline to Week 6 in the MADRS total score was -9.01 in the Rejoyn group compared with -5.39 in the Sham group, which yielded a treatment group difference of -3.62 (p = 0.0099, 95% CI [-6.36, -0.88]) (see Figure 11).

Figure 11: LS Mean Change from Baseline during Treatment Period in MADRS Total Score in the Subgroup with Baseline GAD-7 Total Score ≥10, MMRM (mITT)



* P-value < 0.05, ** P-value < 0.01
Note: Error bars are LS Mean +/- One SE.

MADRS - Extension Phase

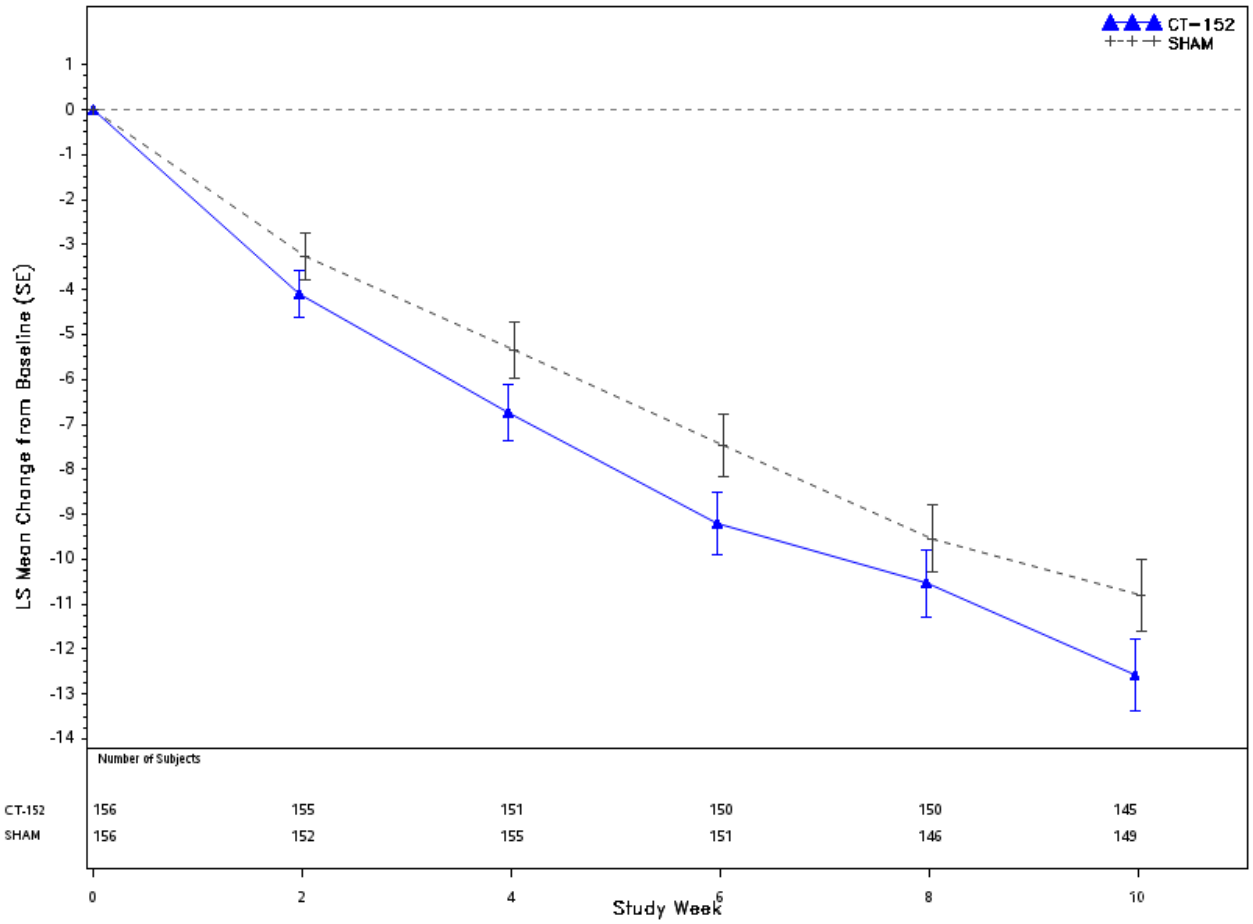
In the mITT, the treatment effect of Rejoyn persisted past Week 6 with a trend favoring continued improvement. The mean change from baseline to Week 10 in MADRS total score was -10.96 in the Rejoyn group compared with -9.93 in the Sham group, which yielded a group difference of -1.03. This between-group difference was not clinically significant.

In the MADRS Anxious Subgroup, the mean change from baseline to Week 10 in MADRS total score was -11.48 in the Rejoyn group compared with -9.31 in the Sham group, which yielded a group difference of -2.18.

MADRS - Adherent Subgroups

Participants were considered adherent to the digital therapy if they completed at least 12 of 18 treatment sessions. In participants who were deemed “adherent”, the mean change from baseline to Week 6 in MADRS total score in the mITT was -9.21 in the Rejoyn group compared with -7.47 in the Sham group, which yielded a group difference of -1.74 (p = 0.0721, 95% CI [- 3.65, 0.16]). At the end of the extension period, the mean change from baseline to Week 10 in MADRS total score was -12.58 in the Rejoyn group compared with -10.8 in the Sham group, which yielded a group difference of - 1.78. This suggests a durable effect (see Figure 12). A high percentage of participants met this definition of adherence (88.1% for both groups).

Figure 12: LS Mean Change From Baseline in MADRS Total Score for Participants Who Completed 12 or More Treatment Sessions, MMRM (mITT)



Note: Error bars are LS Mean +/- One SE. (p-values are not available for Weeks 8 and 10)
Weeks 1 through 6 represent the treatment period. Weeks 7 through 10 represent the extension period.

In participants who were fully adherent to the recommended 6 week treatment course, completing 18 out of 18 sessions, the mean change from baseline to Week 6 in MADRS total score was -9.44 in the Rejoyn group compared with -7.48 in the Sham group, which yielded a group difference of - 1.95 (p = 0.1438, 95% CI [-4.58, 0.67]). At the end of the extension period, the mean change from baseline to Week 10 in MADRS total score was -13.98 in the Rejoyn group compared with -10.61 in the Sham group, which yielded a group difference of -3.37. A considerable percentage of participants were fully adherent (43.5% and 42.4% for Rejoyn and Sham, respectively). In sum, this MADRS adherence subgroup analyses suggest that participants who were adherent to the recommended number of sessions (or adherent per protocol) had a greater therapeutic effect that sustained over time.

Overall, out of the 18 total treatment sessions, the mean number of sessions completed was 15.1 for Rejoyn compared with 15.4 for Sham.

Participant and Healthcare Professional Satisfaction

Participant satisfaction and Healthcare Professional (HCP) satisfaction with Rejoyn were assessed by ratings on the Subject Satisfaction Scale (SSS) and HCP Satisfaction Scale (HCP- SS), respectively, at the end of the treatment period (Week 6). Participants in the Rejoyn group had a favorable impression of the treatment session experience with 85% rating the experience as “extremely satisfied” (37.1%) “satisfied” (38.9%), or “somewhat satisfied” (9%).

Investigators in the Mirai Trial had a favorable impression regarding the convenience of software to deliver treatment with 82.4% rating the convenience as “extremely convenient” (18.7%), “convenient” (49.7%) or “somewhat convenient” (14.0%).

SUPPORT

For additional support with any aspect of the Rejoyn app, you can contact Rejoyn support via phone at 1-833-973-5696.

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